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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/723,000	11/27/2000	Jorg J. Goronzy	07039-170002	4888

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EXAMINER	
BROWN, STACY S	
ART UNIT	**PAPER NUMBER**
1648	15

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/723,000	GORONZY ET AL.	
	Examiner	Art Unit	
	Stacy S Brown	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-57 and 60-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-57 and 60-62* is/are rejected.

7)☒ Claim(s) *61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 November 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment filed July 15, 2002 is acknowledged and entered. Claims 48-57 and 60-62 are pending and examined on the merits.

Specification

2. The specification, page 14, contains a list of sequences. These sequences appear to match with the sequence listing of the application. The sequence listed on page 14 should be notated with their respective sequence identifiers.

Claim Objections

3. Claim 61 is objected to for having a grammatical error, "the a polymorphism".

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48-57 and 60-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the determination of developing severe disease by detecting the presence or absence of some polymorphisms in the HLA-DRB1 allele, does not reasonably provide enablement for the determination of developing severe disease by detecting the presence or absence of any polymorphism in the HLA-DRB1 allele. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The nature of the invention is drawn to a method of determining whether a patient will develop severe rheumatoid arthritis based on the presence or absence of polymorphism(s) in an HLA-DRB1 allele in a patient already suffering from RA. The breadth of the claims is unreasonable, encompassing the detection of any polymorphism and correlating it to the likelihood of developing severe RA. The specification fails to provide guidance for correlating any random polymorphism to the method of determining a predisposition to severe RA. The specification sets for three polymorphisms that correlate with RA associated alleles on page 4, lines 18-20. Further discussion of the prior art continues on pages 28-32, where different models based on the "shared epitope" theory are referred to. The "shared epitope" spans positions 67-74 of the HLA-DRB1 allele and is associated with RA (page 28, lines 2-3). Therefore, given the breadth of the claims, the state of the art, the lack of working examples and the lack of guidance in the specification for correlating any polymorphism with predicting disease severity, the claims are only enabled for certain polymorphisms.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48-57 and 60-62 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 48, "determining the predisposition" is unclear because there are no endpoints that indicate what qualifies as a patient being predisposed. Further, "severe" disease is a relative term. If this term is known in the art and known to be a particular set of symptoms, Applicant is requested to point out the known definition of "severe" disease.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 48-57 and 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goronzy *et al* (*J. Clin. Investigation, Inc.* 1994, 94:2068-2076) in view of Abril *et al* (*Arthritis Rheum.*, 1998, 40:762). The claims are drawn to a method of determining the predisposition of a rheumatoid arthritis patient to develop severe disease comprising 1) comparing the frequency of $CD4^{+}/CD28^{null}$ cells to a reference frequency and 2) determining the presence/absence of a polymorphism in an HLA-DRB1 allele in a patient. The patient is from a population of patients having diffuse rheumatoid arthritis condition, follicular rheumatoid arthritis condition, granulomatous rheumatoid arthritis condition; the population comprises healthy individuals, individuals having subcutaneous nodules, extra-articular involvement and major joint destruction. Also claimed is a kit comprising a binding pair member that binds to a cell marker, a primer that binds to the locus containing an HLA-DRB1 allele, and a reference chart.

Goronzy teaches that the $CD4^+$ T cells are important in inducing and sustaining the synovial inflammation. Goronzy also shows the characterization of RA patients' HLA-DRB1 alleles by amplification with primer sets specific for a sequence polymorphism of the HLA-DRB1 alleles (pages 2068-2069). Also disclosed is that most patients with Felty's syndrome and patients with other extra-articular rheumatoid organ manifestations have a twice as many disease associated HLA-DRB1 alleles. Goronzy fails to teach the determination of the frequency of $CD4^+/CD28^{null}$ cells.

However, Abril teaches that CD28 deficient $CD4^+$ T cells "appear to play a critical role in the disease process leading to RA, suggesting that genes controlling the expression of $CD28^-$ [deficient] T cells represent novel disease risk genes in RA." One of ordinary skill in the art would have been motivated to use the teachings of Abril in Goronzy's method of analyzing the presence of $CD4^+$ T cells and clonal expansion of T cells. One would have been motivated by Abril's teaching that CD28 deficient cells represent risk genes in RA. One would have had a reasonable expectation of success that the method and materials of Abril would have worked in Goronzy's method because both are looking at $CD4^+$ T cells' role in RA progression.

Regarding the populations of patients and their symptoms, one of ordinary skill in the art would have been motivated to treat a patient having those symptoms with the combined method of Goronzy and Abril. The symptoms and populations are representative of known characteristics of RA and testing protocol (examining healthy patients).

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

7. No claim is allowed.

Papers relating to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 located in Crystal Mall 1. The Fax number for Art Unit 1648 is (703) 308-4426. All Group 1600 Fax machines will be available to receive transmissions 24 hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Stacy S. Brown, whose telephone number is (703) 308-2361. The Examiner can normally be reached on Monday through Friday from 6:30 AM-4:00 PM, (EST). If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, James C. Housel, can be reached at (703) 308-4027. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SSB

Stacy S. Brown
May 15, 2003

James C. Housel 5/17/03
JAMES HOUSEL
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